

Lung Donor Selection and Management

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Lung transplantation is still limited by the shortage of suitable donor organs. This results in long waiting times for listed patients with a substantial risk (10–15%) of dying before transplantation. All efforts to increase donor awareness through legislation, public campaigns, and training of transplant coordinators and medical ICU staff should be encouraged. Only a minority of cadaveric donors meets the preset ideal lung donor criteria, leaving many transplantable lungs untouched. Donor lung utilization can be further improved by careful selection of extended criteria donors, by active participation of transplant teams in donor management, and by verifying as often as possible the quality of lungs in the donor hospital by a member of the transplant team. This article aims to update the current evidence from the literature to identify and select potential lung donors and to manage cadaveric donors to maximally increase the organ yield for lung transplantation.

Keywords: lung transplantation; extended criteria; organ donor; donor management

Over the last 25 years, lung transplantation has been an appropriate option for well-selected patients suffering from different types of end-stage lung disease refractory to medical management, thereby improving survival and enhancing quality of life. This form of surgical treatment has enjoyed increasing success, with better early and late survival over the last decade (1).

As a result of its own success with a proliferation of transplant programs in every country and an extension of the indications with more patients listed, the main limiting factor to the widespread application of lung transplantation has now become the shortage of suitable donor organs, resulting in longer waiting times for listed patients with a substantial risk of dying before transplantation. Waiting list mortality may vary among transplant centers and countries. Based on data from Organ Procurement and Transplantation Network (OPTN) as of July 10, 2008 (www.OPTN.org), more than 2,100 patients are currently listed for lung transplantation in the United States, while 1,466 received a suitable cadaveric organ and 276 patients (about 13%) died awaiting transplantation in the year 2007 (2). In the same year, 849 patients were registered on the lung waiting list in Eurotransplant. Five hundred one patients received a transplant, while 124 (about 15%) died awaiting a suitable lung offer (3). Mortality on the waiting lists is highest among patients with pulmonary fibrosis, cystic fibrosis, and pulmonary hypertension, and is lowest in patients with emphysema (4). It has been postulated that lung allocation algorithms should therefore take into account the medical urgency, prioritizing patients with an increased risk of dying on the waiting list

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(5, 6). It is still not clear whether the new Lung Allocation Score (LAS) recently implemented in the United States will result in a decreased waiting list mortality (7).

All initiatives to increase donation rates should be encouraged: legislative action, public education and campaigns, and professional training programs. All the above may influence the enormous differences that exist in the number of organ donors per million of population (pmp) worldwide. A striking difference is seen within Eurotransplant, the organ exchange organization distributing organs to patients residing in Austria, Belgium, Germany, Croatia, Luxembourg, The Netherlands, and Slovenia. Countries with an opting-out legislation (presumed consent law in Belgium and Austria) have nearly doubled the number of organ donors, reaching 20–30 pmp compared with countries with an opting-in legal system (informed consent law in the Netherlands and Germany with 10–15 organ donors pmp) (3).

Currently, the majority of organs come from patients who are certified as brain dead and whose relatives agree to organ donation. Most multiorgan donors become brain dead as a result of a head trauma. Other causes include cerebrovascular accidents, including spontaneous intracerebral bleeding and thrombosis, brain tumor, and anoxic, metabolic or toxic brain injury. Lungs from brain-dead donors are fragile and more sensitive to traumatic situations compared with other organs. Lungs may get injured in the hours before and after brain death resulting from direct trauma, resuscitation maneuvers, neurogenic edema, aspiration of blood or gastric content, or ventilator-associated trauma and pneumonia, making them unsuitable for transplantation (8–10). A high prevalence of pulmonary arterial thrombosis/embolism is seen in donor lungs rejected for transplantation (11). These are reasons why many donor lungs have become unsuitable for transplantation at the time of offer. It is estimated that lungs are recovered in only 15 to 25% of multiorgan donors. A recent study from Canada reported a utilization rate of 23% (12). In an analysis by the California Transplant Donor Network, more than 85% of the lungs were excluded for several reasons (13). Out of 2,139 cadaveric donors reported to Eurotransplant in the year 2007, only 503 (23.5%) served as lung donors (3). This percentage was lower compared with other solid organs (kidney: 90.2%; liver: 73.3%; heart: 28.0%).

Various strategies to overcome the potential lung donor pool have therefore been explored successfully in the recent decade (14, 15). Living donor lobar lung transplantation has been offered to a small number of patients with advanced lung disease (16, 17). Cadaveric lobar transplantation, split lung transplantation, and peripheral segmental resection have all been described as reliable procedures for downsizing donor lungs in case of size discrepancy (18, 19). Contralateral lung transplantation has been reported to overcome unilateral donor lung problems (20). Recently, lungs recovered from controlled (21, 22) and also uncontrolled non-heart-beating donors (23, 24), also called donors after cardiac death, have been transplanted successfully (25). *Ex vivo* lung perfusion and reconditioning holds potential promise to further increase the number of donor lungs initially deemed unsuitable for transplantation (26, 27).

Despite these measures, there are still too few organs to help all those in need of transplantation. Therefore, the available cadaveric donors must be selected and managed judiciously to maximize the utilization of this precious resource.

DONOR SELECTION

Rationale for Proper Donor Selection

It is well known that different insults to the donor lung before and after declaration of brain death, preservation, transplantation process, and reperfusion in the recipient all play an important role in the development of ischemia-reperfusion injury (28), recently properly defined as primary graft dysfunction (PGD) by a working group within the Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT) (29). PGD occurs in various degrees in about 10 to 50% of transplant recipients (30) and is responsible for nearly one third of the early deaths in the first 30 days after the procedure (1). The impact of donor factors appears predominant in the initial 24 hours after reperfusion, whereas recipient risk factors such as pre-existing pulmonary hypertension become more important thereafter (31). The impact of donor factors can be differentiated into those that are inherent to lung donor characteristics (such as age, smoking history, race, sex, and underlying lung disease) and those that are acquired in the moments before brain death (traumatic contusion, hemodynamic instability, blood transfusions) or in the hours thereafter (neurogenic edema, mechanical ventilation, bronchoaspiration, atelectasis, pneumonia). This distinction is important, as adequate donor management could potentially influence these acquired problems. A detailed review of published data analyzing donor-related risk factors for the development of PGD was recently published by de Perrot and colleagues on behalf of the ISHLT working group (32).

Minimizing the risk of PGD by adequate donor selection and early management is therefore of utmost importance to achieve good early results after lung transplantation.

Lung Donor Criteria

During the first decade after the initial successes of lung transplantation in the early 1980s, the criteria used to select lung donors were quite conservative and stringent. The so-called "standard criteria" for choosing the ideal donor are listed in Table 1. These clinical criteria like donor history, age, smoking history, arterial blood gases, chest X-ray, and bronchoscopy findings have often been chosen arbitrarily and have not been substantiated in prospective, controlled trials or even large, uncontrolled trials. Most of the currently available data are based on small, center-specific reports from the early days of lung transplantation (33–42). Evidence to support these

TABLE 1. STANDARD ("IDEAL") LUNG DONOR CRITERIA

Age < 55 yr
Clear serial chest X-ray
Normal gas exchange ($\text{PaO}_2 > 300 \text{ mm Hg}$ on $\text{FiO}_2 = 1.0$, PEEP 5 cm H ₂ O)
Absence of chest trauma
No evidence of aspiration or sepsis
Absence of purulent secretions at bronchoscopy
Absence of organisms on sputum gram stain
No history of primary pulmonary disease or active pulmonary infection
Tobacco history < 20 pack-years
ABO compatibility
No prior cardiopulmonary surgery
Appropriate size match with prospective recipient

Definition of abbreviation: PEEP = positive end-expiratory pressure.

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recommendations, therefore, is often lacking. Acceptability criteria for lung donation were recently reviewed in an extensive consensus report from the Pulmonary Council of the ISHLT (43). The donor factors that were reviewed from the literature included age, graft ischemic time, blood type ABO compatibility, sex, organ size matching, cause of death, duration of mechanical ventilation, radiographic findings, microbial organisms, arterial blood gases, smoking exposure, and donor diagnoses of malignancy. The individual donor will have several factors that may affect post-transplant lung function. These should not be viewed in isolation but rather as interacting variables on a continuum of donor lung acceptability, from the ideal donor over the extended donor to the unusable donor (44).

Age. Older studies investigating the effect of older donor age on survival using the ISHLT database found lower early and late survival (45, 46). When older donor age was combined with graft ischemic times longer than 6 hours, this effect was amplified. Three single-center studies have focused specifically on donor age greater than 50 to 60 years. Similar short- and long-term outcomes compared with recipients of lungs from younger donors were reported by the Hannover group (47) and the Gothenburg group (48). The authors from the Toronto group also did not find a difference in hospital mortality related to donor age. However, they reported a lower 10-year survival related to older donor age and more recipients from older donors dying from bronchiolitis obliterans (49). According to the most recent analysis of ISHLT registry analyzing data between 1995 and 2005, donor age is only a borderline risk factor ($P = 0.083$) for 1-year mortality but still a significant factor ($P = 0.008$) for 5-year mortality (50). The fact that older donor lungs may have been preferentially allocated to older recipients with increased morbidity may have influenced this finding. Older donor age alone should not be a strict criterion to reject older lungs, as their macroscopical appearance often suggests better quality in never-smokers compared with smokers of younger age.

Graft ischemic time. As for age, the upper limit of acceptability for cold ischemic times remains unclear. Historically, most transplant centers preferred an ischemic time limited to 4 to 6 hours. A negative effect on survival with ischemic times beyond 5 hours was found in a single-center report from Melbourne (51). Thabut and colleagues in a French multicenter analysis demonstrated poorer early gas exchange beyond an ischemic time of 5.5 hours independent of the preservation solution used (52). The hazard ratios for death at 1 year after bilateral lung transplantation were 2.7 with ischemic times exceeding 8 hours and 7.1 after 10 hours. This finding could not be confirmed in other studies (45, 53) except when combined with older donor age (> 55 yr) (53). According to the recent ISHLT registry data, graft ischemic time is not an increased risk factor for 1- and 5-year survival after lung transplantation (50). Interestingly, in lung recipients with emphysema the relative risk of dying within the first year drops below 1.0 if ischemia time extends more than 4 hours. Since most transplant teams have switched to an extracellular solution for lung preservation, good results have now been reported with ischemic times greater than 10 hours. An expected long ischemic time *per se* should not be considered an absolute contraindication to accept otherwise healthy lungs from a long-distance donor.

ABO compatibility. Transplantation of solid organs that are not ABO compatible typically results in hyperacute rejection, leading to immediate graft failure and death. Patients with preformed donor-specific human leukocyte antigen (HLA) antibodies will need a negative prospective lymphocytotoxic

cross-match before transplantation to avoid the risk of hyperacute rejection. Two reports have compared the outcome after lung transplantation from ABO-identical versus ABO-compatible donors (54, 55). A small survival advantage in ABO-identical recipients was noted in one study looking at outcome after retransplantation (55). Although ABO compatibility is not an increased risk factor in the ISHLT Registry data, recipients with more than four HLA mismatches have an increased relative risk of dying within the first year (1.18 times higher) and at 5 years (1.23 times higher) after the transplant (50). In conclusion, no significant disadvantages are expected to occur when using ABO-compatible rather than ABO-identical donors in first transplant recipients. New preservation techniques in the future that allow longer ischemic times may help to span the time window that is needed for HLA matching in all recipients.

Sex. Although sex matching between donor and recipient does not appear as a criterion in the standard list, a female donor to female recipient status is associated with a decreased relative risk of 0.91 for 5-year mortality in the 2007 ISHLT registry (50). A recent analysis showed that female to male transplant, even after adjusting for size mismatch and diagnosis, was associated with higher 30-day mortality, whereas female to female was beneficial (56). A multicenter study in France also found that donor and recipient sex mismatch was significantly associated with decreased long-term survival (57). The underlying reason for these sex differences remains unclear.

Size matching. Typically, smaller grafts are selected for recipients with smaller thoracic cavities and larger lungs for those with larger chest size. At most centers, size matching between donor and recipient is based on donor and recipient height and/or predicted total lung capacity. The Papworth group reported on 20 heart-lung recipients with a donor to recipient difference in predicted total lung capacity (TLC) of at least 1 L. Ten patients received smaller lungs with a predicted TLC of 75% and 10 others were grafted with larger lungs with a predicted TLC of 125% (58). No clinical problems were reported and the postoperative measured TLC, FVC, and FEV₁ were close to those predicted for the recipient. Based on these data, donors with a predicted TLC of 75 to 125% of the predicted TLC of the recipient can probably be safely used. Lung reduction at the time of transplantation of lungs that are grossly oversized is possible by performing a lobectomy before implantation or by stapling of peripheral lung tissue before closure of the chest with no reported postoperative complications associated with this additional procedure (59).

Cause of death. Few studies specifically addressed differences in outcome in relation to the donor cause of death. In a study by the St. Louis group, a higher incidence of both acute and chronic rejection was observed in lung recipients from donors with trauma-induced brain death as compared with other causes of brain death (60). This may be related to up-regulation of proinflammatory cytokines after brain injury affecting the inflammatory status of the lung, increasing the risk for primary graft dysfunction and other immune-mediated complications. In another study from the Newcastle group, traumatic donor death did not affect early graft function and recipient outcome was comparable between traumatic and nontraumatic donors (61). According to the latest ISHLT report, cause of death is not a discriminator for 1-year mortality. However, patients receiving lungs from donors dying from anoxia have a decreased risk (RR 0.72) for 5-year mortality (50). Currently, there are insufficient data to exclude any donor for lung donation for reason of the cause of brain death.

Duration of mechanical ventilation. Potential donors on mechanical ventilation for prolonged periods are at an in-

creased risk for ventilator-associated pneumonia. Ruiz and coworkers found that duration of donor ventilation correlated strongly with the presence of infection with 90.5% of donors ventilated longer than 48 hours being infected (62). No increase in recipient infection with organisms identified in the donor lung, however, was observed with donor lungs used as long as 15 days after the initial intubation in another study (63). No data on the effect of length of donor ventilation are available in the ISHLT registry slides (50). There is no indication that donors should be excluded solely on the basis of the length of mechanical ventilation.

Radiographic findings. Serial standard portable chest X-rays are usually taken as part of the evaluation of a potential lung donor. However, it is important to recognize that plain chest X-rays taken at the bedside are far less sensitive than computed tomographic scanning and may underestimate structural abnormalities such as minor contusions or small infiltrates. The predictive value in accepting or rejecting the lung was low and the interobserver variability was high in a retrospective study from Johns Hopkins (64). As these donor chest X-rays are often interpreted by an inexperienced person, it is important to give proper training to those involved in donor care (65). There is a paucity of data to establish firm guidelines regarding chest X-ray findings. Donors with strong unilateral abnormalities on chest X-ray should not be excluded for donation of the contralateral lung (66). McCowin and coworkers have shown that 37% of donors have infiltrates on the initial film, of which 51% resolved completely after proper donor management (67). Diffuse bilateral lung infiltrates are highly suspicious for a developing pneumonia, especially in a patient with high temperature and purulent secretions. These lungs should not be used if heavy, pneumonic infiltrates are confirmed during organ retrieval. In conclusion, evaluation of a donor chest X-ray is a highly subjective process, and as an isolated criterion has a limited role in the determination of organ suitability. No data are currently available in the literature regarding the value of a high-resolution CT scan to differentiate an acceptable from an unacceptable lung donor.

Gram stains and bronchoscopy findings. Sputum Gram stains and cultures are usually obtained on all lung donors either by suction catheter or bronchoscopy. Studies have shown that a positive donor Gram stain did not predict posttransplant pneumonia, oxygenation, or duration of post-transplant mechanical ventilation (68–70). The incidence of donor infection was reported to be 52% and transmission to the recipient occurred in 8.1% despite appropriate antibiotic prophylaxis (62). A study from the Newcastle group reported poor early graft function and decreased survival in a group of patients with positive cultures of donor bronchoalveolar lavage (BAL), suggesting that lower airway colonization may be indicative of an increased risk for postoperative graft infection and dysfunction (71). Therefore, the impact of microbial colonization or subclinical infection in assessing the donor lung is not clear. Successful transplantation is possible with frequent postoperative microbial airway sampling and adequate antibiotic treatment against the organisms identified.

Gas exchange. Good oxygenation is believed to be the most important indicator for the functional quality of the lung. Arterial blood gas analysis in a donor with an indwelling arterial catheter can be easily repeated to follow the evolution in gas exchange in the interval between brain death and organ retrieval. The PaO₂/FI_{O₂} ratio can be easily affected by reversible processes such as retained secretions, pulmonary edema, and atelectasis. Aggressive donor management with specific donor interventions (*see below*) is therefore important and initially poor gas exchange values should not immediately exclude any

donor. It remains unclear how low the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio for donors can be without affecting transplant outcome. In a French multicenter study, donor gas exchange before harvest was significantly associated with early and long-term outcome (57). Moreover, there was a steep increase in the relative risk of death when the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio was below 350 mm Hg. Luckraz and coworkers found higher 30-day mortality but similar overall mortality in a group of recipients with a donor $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ between 225 and 300 mm Hg (72). Successful transplants, however, with donor lungs with ratios less than 300 mm Hg have been reported (73). In donors with unilateral abnormalities on chest X-ray, initially low arterial blood gases may significantly improve after exclusion of the unacceptable lung intraoperatively (66). Direct left and right pulmonary vein blood gas sampling may also be helpful in (re)assessing the lungs individually immediately before pulmonary flush (74), and partial pulmonary vein oxygen pressure was reported to correlate much more reliably with outcome in the recipient than Pa_{O_2} (75). Much higher oxygen values are then often measured compared with samples taken from the radial artery catheter with the donor still in the intensive care unit (76). Therefore, a low $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio alone is not a good criterion to decline donor lungs for transplant suitability.

Smoking. The major concern for using donors with a history of cigarette smoking is the potential for poor lung function due to the obstructive pulmonary disease and the risk of transplanting an undetected primary or metastatic cancer or for developing a malignancy in the donor lung in the years after the transplant (77, 78). Careful examination of the chest X-ray, and computed tomographic chest scan whenever available, as well as meticulous examination of the lung and biopsy of any suspicious lesions in the operating room at the time of organ retrieval, are of prime importance to limit the risk of lung cancer transmission (78). In one older study, no difference was found in outcome from donors who smoked more than 20 years (79). Another study found that donor history of smoking affected early, but not late outcome after lung transplantation in terms of oxygenation, ventilation time, and intensive care unit stay (80). Moreover, these variables were dose dependent. There are, however, no studies that directly address how much cigarette smoke exposure a donor may have before the lungs are not safe to use for transplantation. A donor history of smoking should therefore not prevent the use of donor lungs for transplantation. Emphysematous changes with apical blebs or postinfectious scar lesions are often seen in these older donors, but these can easily be resected at the time of implantation.

Donor history of cancer. Tumor transmission after solid-organ transplantation can lead to devastating and lethal consequences because of the rapid tumor dissemination in a patient under immunosuppressive therapy. The use of a donor with an active malignancy, sometimes not previously known until detected on biopsy of a suspicious lesion at the moment of organ retrieval, is not acceptable except for a few special cases in which the risk of tumor transmission is deemed very low (basal cell skin cancer, some squamous cell cancers, *in situ* carcinoma of the cervix, primary central nervous system tumors with the exception of medulloblastomas, glioblastomas, and high-grade astrocytomas) (81–83).

From the literature review on all clinical donor factors given above, it is clear that the currently accepted standard criteria were based on a very limited body of literature and that there are no evidence-based data to provide firm guidelines to determine lung donor suitability. Each of the standard lung donor criteria currently in use should be further analyzed using multicenter data from a well-designed database (84). The voluntary ISHLT Registry is currently the best tool to analyze the individual clinical donor risk factors (1).

Donor lung scoring and biomarkers

As current selection criteria are largely subjective and have poor predictive power for early outcome in the individual recipient, there is a need for more objective lung donor assessment tools (85, 86).

The development of a lung donor score may further help in weighing overall donor lung quality that could possibly predict donor selection and early post-lung transplant outcome. Such a score would also allow comparison between institutional reports. The Melbourne group recently published on the feasibility and utility of a lung donor score using five clinical donor variables available at the time of donor selection (age, smoking history, chest X-ray, secretions, and arterial blood gas results) (87). Each variable was divided into four levels, allowing a score between 0 and 20. The authors concluded that this score was significantly associated with early outcome, at least after double lung transplantation. The Toronto group recently applied the donor score retrospectively in a larger number of patients and failed to find a similar correlation between donor score and early post-transplant outcome (88). Multicenter collection of donor demographics and outcome data will be needed to further design a robust scoring system for donor lung quality that is accepted worldwide to allow comparison between transplant centers.

Some groups have focused on measuring biologic markers in the donor lung as a predictor of outcome. Fisher and colleagues from the Newcastle group studied interleukin-8 (IL-8) in donor BAL and found a strong correlation with the lowest $\text{PO}_2/\text{Fi}_{\text{O}_2}$ ratio and early mortality in the recipient (89). Kaneda and coworkers from the Toronto group demonstrated that IL-6, IL-8, TNF- α , and IL-1 β in BAL fluid during the cold ischemic period were risk factors and that IL-10 and IFN- γ were protective factors that correlated with 30-day mortality while no single clinical donor variable did so. Moreover, the ratio of IL-6/IL-10 was the most predictive for primary graft failure and death (90). The availability of rapid assays to measure these inflammatory markers of lung graft injury are needed to become useful for more accurate decision making regarding lung acceptance, for better recipient matching, and for targeted post-implantation management.

In situ inspection and *ex vivo* lung evaluation

Studies assessing unsuitable, unused lungs have found that more than 40% would have been potentially suitable for transplantation (13, 91–94). Physical examination of the pulmonary graft at the donor hospital during organ retrieval by an experienced transplant surgeon is in our opinion still the best method to assess for lung injury and transplant suitability. This allows the surgeon to personally check the chest X-ray in the donor hospital and to repeat the bronchoscopy to clear the airways from secretions and to take specimens for bacteriologic, cellular, or immunologic examination. Lungs can be directly inspected for zones of atelectasis, hemorrhagic contusion, edema, or pneumonic infiltration. Lung compliance can be tested under direct vision with the so called “collapse test” by disconnecting the endotracheal tube from the ventilator. If lungs remain inflated or only slowly collapse, this may be a sign of interstitial fluid accumulation, pneumonia, or small airways obstructive disease (emphysema) or major airway plugging. Lungs can be gently reinflated, thereafter removing all atelectatic zones by asking the anesthetist to squeeze the lungs. A blood gas sample can then be drawn from left and right pulmonary veins to reassess the oxygenation capacity from both lungs separately after the previous maneuvers (74). By making the effort to travel to the donor hospital and to evaluate the

lungs *in situ* whenever possible, we were able to increase our lung acceptance rate in the last 2 years up to 41% of all effective organ donors procured in our donor hospital network (95). Many more lungs were found suitable for transplantation than originally believed at the time of lung offer. This policy was logically possible because of the manpower in our department (with two staff members on call for transplants) and because of the short distances between our transplant center and the referring donor hospitals.

If the time interval between harvesting and implantation of the lungs could be safely prolonged, this would create a window to further test lung function and viability in the recipient hospital before the patient is anesthetized for the transplant procedure. *Ex vivo* human lung reperfusion is a new technique that allows for careful visual inspection of the explanted lungs, hemodynamic and ventilatory measurements, and evaluation of gas exchange. The setup that was used in our laboratory to evaluate human lungs declined for primary transplantation has previously been published (15, 27). Briefly, the closed circuit contains a blood reservoir, a centrifugal pump, a leukocyte filter, a gas exchanger, an inline blood gas analyzer, and a heater/cooler. An endotracheal tube and perfusion cannulas are inserted for inflow of venous blood through the pulmonary artery and outflow of saturated blood from the left atrium. Lungs are mounted in a Plexiglas box and reventilated and blood reperfused for functional assessment with measurement of gas exchange, hemodynamic and aerodynamic parameters, and indicators of lung edema (96). Other groups have also published their initial experience using a similar *ex vivo* reperfusion set up (97, 98).

Beside (re)assessment of donor lungs, *ex vivo* lung perfusion as a technique is hoped to bring new applications that may expand the donor pool and change clinical practice in the future, including *ex vivo* repair of damaged lungs, prolonged organ preservation, and *ex vivo* conditioning against allograft rejection. Many more experiments are needed and portable devices should be developed by biomedical companies before these potential applications will become a clinical reality.

Extended criteria donors. To overcome the critical organ shortage and to decrease the mortality rate on their waiting list, many transplant programs have relaxed their original ideal donor criteria, now also using extended criteria donors, often named marginal donors (73, 79, 95, 99–106).

An overview of the published results is summarized in Table 2. The percentage of marginal donors in reported series ranges between 24% (105) and 77% (103). The percentage of extended donors failing to satisfy two or more criteria varies between 8% (79) and 38% (102). Seven reports (73, 79, 95, 101–103, 105) suggested equivalent outcome with respect to early morbidity and mortality, postoperative time on ventilator and time in ICU, hospital stay, 30-day survival, pulmonary function, and survival at 1 year after the transplant. Two studies, however, have reported a significant difference with inferior outcome in recipients from marginal donors (104, 106). The Toronto group reported a significant increase in early mortality (6.2% in the standard donor group versus 17.5% in the extended donor group at 30 days after lung transplant). Mortality was highest (22.2%) in recipients that did not meet the standard guidelines as defined by the ISHLT (older age, colonization with *Burkholderia cepacia*) (104). Recipients of marginal lungs in the report from the Newcastle group had a higher incidence of severe (grade 3) primary graft dysfunction (43.9% versus 27.4%) and 90-day organ-specific mortality (15.7% versus 5.1%), and higher 30-day mortality in bilateral (17.0% versus 2.7%) but not single-lung recipients (106).

Authors have suggested that extended donor lungs, especially with pulmonary infiltrates or contusion, should be used primarily for double-lung replacement in recipients with emphysema. Caution is warranted in patients with pulmonary hypertension, especially in case of single-lung transplantation, because of the postoperative perfusion imbalance with an increased risk of reperfusion-related pulmonary edema in the graft aggravating the already existing donor lung dysfunction (101). Similarly, some degree of reversible donor lung dysfunction is usually tolerable in single-lung transplantation for emphysema, in which the native lung can oxygenate satisfactorily until the graft recovers. One study has found that

TABLE 2. PUBLISHED SERIES ON EXTENDED CRITERIA DONORS

First Author	Kron	Sundaresan	Gabbay	Bhorade	Straznicka	Pierre	Lardinois	Aigner	Botha	Meers
Center	Charlottesville	St. Louis	Melbourne	Maywood	Sacramento	Toronto	Zurich	Vienna	Newcastle	Leuven
Year	1993	1995	1999	2000	2002	2002	2005	2005	2006	2008
Reference	99	101	102	79	103	104	73	105	106	95
Marginal (total) n	10 (28)	44 (133)	64 (112)	52 (113)	129 (167)	63 (123)	63 (148)	23 (94)	83 (201)	27 (50)
% marginal	35	33	57	46	77	51	43	24	41	54
Age > 55 yr	N.S.	2	4	9	10	9	12	5	17	9
Smoking > 20 pack-yrs	N.S.	9	5	15	3	26	20	1	32	12
Chest X-ray abnormal	6	34	39	5	34	41	29	3	21	10
PaO ₂ < 300 mm Hg*	0	6	20	0	32	0	15	8	11	2
Purulent secretions	8	N.S.	24	0	8	8	14	N.S.	14	N.S.
Inhaled drugs	N.S.	N.S.	N.S.	20	13	N.S.	N.S.	1	N.S.	N.S.
Ventilation > 5 d	N.S.	N.S.	N.S.	7	N.S.	27	N.S.	N.S.	19	N.S.
1 criterion only	N.S.	37	40	48	100	48	N.S.	18	58	23
2 criteria	N.S.	7	20	4	29	10	N.S.	5	19	7
3 criteria	N.S.	0	4	N.S.	N.S.	5	N.S.	N.S.	6	1
Hospital outcome	9/10 survivors	=	=	=	†	=	=	†	=	=
Early outcome (1 yr)	N.S.	=	=	=	N.S.	=	=	=	=	=
Intermediate outcome	N.S.	=	=	N.S.	=	N.S.	=	N.S.	=	N.S.

Definition of abbreviation: N.S. = not stated.

* Inspiratory oxygen fraction = 1.0, positive end-expiratory pressure of 5 cm H₂O.

= Identical outcome.

† Different outcome compared with standard donors.

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cardiopulmonary bypass appeared to be necessary to facilitate second graft implantation in bilateral lung transplantation more often in the marginal donor group than in the ideal donor group (101). To minimize the requirement for cardiopulmonary bypass in bilateral transplants, it is therefore recommended to explant the less functioning of both recipient lungs first or to start with the implantation of the more “acceptable” donor lung. The Toronto group stated that the increased mortality risk in their patients by using lungs from marginal donors was justified, as waiting time is long and thus mortality on the waiting list is high in their transplant center (104). Caution, however, is warranted, especially in donors with bilateral infiltrates on chest X-ray, not related to atelectasis, or with truly purulent secretions. Finally, the authors pointed out that the experience of the retrieval surgeon is critical to a good outcome when using extended donor lungs (104).

Improved lung preservation techniques and the use of extracellular type flush solutions have resulted in a decrease in the incidence of severe ischemia-reperfusion injury and a better early outcome in recent years. This may also allow use of more extended donors with less optimal grafts.

DONOR MANAGEMENT

Brain Death and Lung Injury

Understanding the pathophysiologic mechanisms of donor lung injury resulting from brain death are essential in the treatment of a lung donor. As previously stated, lungs may get injured in the hours before and after brain death resulting from direct trauma, resuscitation maneuvers, neurogenic edema, aspiration of blood or gastric content, or ventilator-associated trauma and pneumonia (8–10).

Brainstem death is associated with an autonomic crisis, the so called sympathetic storm, whereby a boost of noradrenaline is released in the circulation. This will result in acute systemic vasoconstriction and a rise in systemic vascular resistance. As a consequence, left ventricular output will decrease and left atrial pressure will rise on one side. Blood volume will be redistributed with an increase in venous return, and so right ventricular output will rise on the other side (107). This sudden increase in pulmonary blood flow leads to higher pulmonary capillary pressures, and development of hydrostatic edema (108). Eventually, failure of the alveolo-capillary membrane, together with direct sympathetic effects, will lead to increased pulmonary capillary permeability and deteriorate pulmonary function (109). These pathophysiologic events have been identified previously as neurogenic pulmonary edema in patients with severe traumatic brain injury. The sympathetic discharge followed by a prolonged period of hypotension also leads to a systemic inflammatory syndrome whereby infiltration of activated neutrophils in the lung will contribute to donor lung injury. Much clinical and experimental work to elucidate the underlying mechanisms of lung injury was performed by the Newcastle group. Fisher and colleagues have found that neutrophil concentration and BAL levels of IL-8 were significantly increased and correlated in potential organ donors when compared with other ventilated control subjects (110). As already mentioned above, these BAL IL-8 levels correlated with early graft failure and mortality after lung transplantation (89). Avlonitis and co-authors reported that in brain-dead rats, early hemodynamic injury during donor brain death determines the severity of primary graft dysfunction after lung transplantation (111). A further study showed that the systemic inflammatory response could be prevented by administration of the α -adrenergic antagonist phentolamine and ameliorated with a vasoconstrictor

given during the neurogenic hypotension that follows the sympathetic boost, suggesting a link between the adrenergic and inflammatory mechanisms of donor lung injury (112). Neyrinck and coworkers found in an *ex vivo* pig lung reperfusion model that donor lung injury was more pronounced in brain-dead heart-beating donors (HBD) compared with sham animals and non-heart-beating donors (NHBD) after 1 hour of warm ischemia, indicating that pathologic changes during the development of brain death are detrimental for post-transplant lung performance (113).

Donor Care

Because the process of potential donor identification, brain death certification, family consenting, and organ procurement may take 12 to 24 hours, it is important to maintain the organ-perfused, though brain-dead body in optimal condition to preserve and optimize the function of all organs to be transplanted. Early contact with the donor referral network will help to improve the lung recovery rate from potential donors (114). Care of the recipient starts with renewed care for organs perfused in a brain-dead donor. Guidelines for the critical care management of the potential organ donor suggests that after the declaration of brain death, treatment strategy previously aimed at cerebral protection should shift toward preserving solid organ perfusion and function (115).

Some principles of donor management apply generally, whereas others are targeted to a specific organ. Because as many organs as possible will be recovered from a given donor, the team in charge of the donor has to consider a treatment in the best interest of all organs. The general management focuses on maintenance of body temperature via external warming, blood pressure, acid/base status, electrolytes, intravascular volume, and prevention of infection.

The process of brainstem death may result in significant hemodynamic, hormonal, and respiratory disturbances that need specific attention to preserve the function of the lungs before retrieval.

Hemodynamic Management

Because of the hemodynamic disturbances resulting from the sympathetic storm at the time of brain death (neurogenic hypertension followed by hypotension), fluid loading can be quite challenging and may contribute to further lung edema and impaired oxygenation if not well monitored (116). Because the disparity between right- and left-sided filling pressures after brain death, CVP monitoring alone to guide fluid loading may be misleading (117). Therefore, the use of a pulmonary artery pressure catheter is advised to optimize filling pressures and monitor cardiac performance and vascular pressures (118). Additional monitoring of extravascular lung water (EVLW) might further guide optimal management of the donor lung. Vasopressors and inotropes may help stabilize the fluctuations in blood pressure to ensure optimal organ perfusion with the lowest possible myocardial oxygen demand. However, the use of catecholamines in the donor was shown to be related to impaired gas exchange in the recipient after transplantation (119). Low-dose vasopressin as an alternative vasopressor has been shown to improve hemodynamics and to reduce inotropic requirements (117), leading to an increased organ yield (120). Furthermore, vasopressin has a similar antiinflammatory effect to noradrenaline in the correction of neurogenic hypotension after brain death (121).

Hormonal Resuscitation

As acute brain death also results in a substantial decrease of several hormones like cortisol, insulin, thyroid, and antidiuretic

hormone levels, replacement before organ recovery may increase graft viability and early recipient outcome (122).

Administration of high-dose steroids to the donor in the hours after brain death has been advocated, as it is believed to reduce the systemic inflammatory response and thus lung injury. The early administration of 15 mg/kg methylprednisolone to the donor resulted in an increased yield and improved oxygenation at organ recovery in a retrospective study at the University of California Davis School of Medicine (123). These findings could not be reproduced in a randomized controlled trial in the United Kingdom (124). Nevertheless, that study demonstrated that the use of steroids was associated with a reduced accumulation of extravascular lung water, even when administered several hours after brain death declaration.

Thyroid hormones including tri-iodothyronine (T3) and L-thyroxine (T4) are commonly used in brain-dead donors (124, 125). The use of T3 may improve donor heart function (126). Improved left ventricular function will result in reduced left atrial pressure, lowering the risk of lung water accumulation. In addition, T3 increases alveolar fluid clearance, a mechanism to reduce lung edema (127). However, a beneficial effect of T3 for the lung donor could not be demonstrated in a randomized controlled trial (124).

Besides aggressive diuresis in donors with fluid overload, pulmonary edema, and diminished gas exchange, stimulation of alveolar fluid clearance (AFC) mechanism may help to improve gas exchange and lung yield. β_2 -adrenergic stimulation with aerosolized terbutaline has been shown to accelerate AFC. In a study using rejected human lungs, Ware and coworkers were able to demonstrate that *ex vivo* administration of aerosolized terbutaline resulted in improved AFC (128). The authors also found that donor treatment with low-dose dopamine was associated with faster AFC and that the administration of diuretics was associated with lower extravascular lung water in explanted lungs. Assessment of AFC might also be a useful tool to extend the donor selection criteria. Our group in Leuven could demonstrate in an *ex vivo* pig lung reperfusion model that terbutaline administered by endotracheal instillation to hydrostatically induced edematous lungs attenuated reperfusion injury by reducing wet to dry weight ratio when compared with a placebo group (129). In a second study comparing HBD versus NHBD, we found that AFC was lower in HBD (8% versus 17%) and that instilled terbutaline improved AFC (130). Interestingly, the increase in ALC was more pronounced in HBD (75%) compared with NHBD (24%) lungs. Similarly, terbutaline resulted in a reduced inflammatory status with reduced TNF- α levels in the donor lung after reperfusion that was more pronounced in the HBD versus the NHBD lungs (A.N., D.V.R.; unpublished data). In a rat lung reperfusion model, Chen and co-authors could demonstrate attenuation of reperfusion injury of warm ischemic lungs by decreasing airway resistance and pulmonary shunt fraction, vascular resistance, and edema (131). Myeloperoxidase activity was decreased and levels of cAMP were increased. No clinical study so far has reported the use of nebulized β_2 -antagonists in human lung donors. Results are awaited of an ongoing multicenter, double-blind, placebo-controlled, randomized study by the California Transplant Donor Network looking at the efficacy of albuterol on oxygenation in brain dead donors (BOLD study: β -agonist for oxygenation in lung donors) (personal communication).

Ventilatory Strategy

Guidelines for the critical care management of the potential organ donor suggest that after the declaration of brain death, treatment strategy previously aimed at cerebral protection should shift toward preserving solid organ perfusion and function (115).

In a multicenter observational survey of 15 care units in Italy, it was noted that no changes to the ventilatory settings and no maneuvers were made after brain death confirmation (132).

A ventilatory strategy with high tidal volumes is potentially harmful and may exacerbate donor lung injury already triggered by the systemic inflammatory response. The use of low tidal volume ventilation was shown to be beneficial in a randomized controlled study for acute lung injury and ARDS when compared with traditional tidal volumes (133). No such trial has been performed to see whether one ventilatory mode is superior to another in the care of the brain-dead organ donor. However, given similarities in the pathophysiologic changes occurring in ARDS and lung injury after brain death, we might expect that beneficial management strategies can be extrapolated.

Recruitment maneuvers are an important component of donor optimization, especially when the oxygenation is subnormal and pulmonary abnormalities are visible on chest X-ray. Atelectasis is a common finding in the lung of cadaveric donors due to prolonged ventilation in the supine position. Prevention of atelectasis will reduce the trauma by cyclic closing and reopening of collapsed lung regions. Recruitment strategies include pressure-controlled ventilation, with an inspiratory pressure of 25 cm H₂O and a positive end-expiratory pressure of 15 cm H₂O for a short interval (2 h) before turning to conventional volume-controlled ventilation with a tidal volume of 10 ml/kg and PEEP of 5 cm H₂O. To prevent loss of alveolar recruitment, higher levels of PEEP should be used immediately after these maneuvers (134). Bronchoscopy should be routinely performed on all potential lung donors to assess for airway damage and visible signs of infection. Regular suctioning of retained secretions through a closed ventilator circuit may be beneficial to improve gas exchange.

Several studies coming from Chicago (135), Cambridge (136–138), and more recently from the University of Texas at San Antonio (139) have demonstrated that the implementation of a specific management protocol for the potential pulmonary donor led to an increased procurement rate without a detrimental effect on early and late survival.

CONCLUSIONS

Liberalization of standard, non-evidence-based donor criteria, and aggressive donor management focused on prevention and correction at best of donor lung injury, can undoubtedly increase the number of lung transplants for all those in need facing long waiting times and risk of premature mortality. Early and long-term outcome in lung recipients, however, should be carefully watched as more extended criteria donors are used. The impact of less perfect donor lungs may be lessened with competent postoperative care in large-volume centers. The outcome for the great majority of recipients will still be much better than not receiving a transplant.

Further prospective, randomized studies are needed to assess the impact of using extended criteria donors and the effect of maneuvers to limit donor lung injury.

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